amendments become necessary because of the Examiner's comments and objection in the final Office Action. Entering of these amendments and withdrawal of the objection are respectfully requested.

B. Rejections under 35 U.S.C. § 103

The rejection of claims 1-4, 6-10, 12 and 17 under 35 U.S.C. § 103, as allegedly being obvious over Ma et al. (European Journal of Immunology 1994, Vol. 24 (1) pages 131-138, "Ma") in view of Adair et al (U.S. Patent No. 5,877,293, "Adair") is respectfully traversed.

The present invention is directed to a method of treating and preventing dental caries by administration of a chimeric antibody that functions via 1) specifically binding to a cariogenic organism, and 2) eliciting a humoral immune response. The Ma reference cited by the Office Action does not teach or suggest the present invention. On the contrary, Ma teaches away from using the method provided by the present invention, *e.g.*, teaches away from using the mechanism recited by the claims of the present invention.

Specifically Ma is directed primarily to expressing a murine IgG1 antibody, Guy's 13, in transgenic plants. According to Ma and the references cited therein, Guy's 13 prevents adherence and colonization of *S. mutans in vivo*. With respect to the functional mechanism of the protective effect of Guy's 13, Ma specifically states that "[t]he protective effect of the mAb *in vivo* is epitope specific, as not all anti-SA I/II mAb were effective [9]" and "[t]he Fc-mediated functions of the mAb were not essential, as the F(ab')2 portion was as protective as the intact IgG,...." (See page 131, bottom of the left column, emphasis added). Ma further concludes at the end of the article that " [a]lthough the maintenance of bivalent antigen binding of the antibody molecule was required for prevention of colonization of *S. mutans in vivo,* the functional Ig regions that are involved in complement binding and opsonization through cellular interactions are not essential." (See page 136, last paragraph). Therefore, Ma clearly teaches that the epitope binding of the Guy'13 antibody is critical to its protective function against *S. mutans* whereas Fc-mediated functions of the antibody such as eliciting a humoral immune response through complement binding or cellular interactions is dispensable since deletion of the Fc region of the Guy's 13 did not have any impact on the protective effect of Guy's 13.

Ma further promotes such teaching by testing the expression of not only Guy'13, but also two other IgG-IgA hybrids of Guy's 13 to see whether the constant region of IgA can enhance the protective effect of Guy's 13. The constant region of IgA does not include a complete Fc region[1], thus does not trigger Fc-mediated humoral immune response in mucosal environment. Ma believes, however, that the constant region of IgA, *i.e.,* Cα2 and Cα3 which contain the J chain and secretory component binding sites increases the valency and resistance to proteolytic activity of the IgG-IgA hybrid antibody and is advantageous, especially when the bacterial aggregation is the important effector mechanism. (See the last paragraph of page 136 and the first paragraph of page 137.) Therefore, by replacing large part of the IgG constant region with the IgA constant region, Ma has truncated the Fc region of IgG and followed its own teaching that the constant regions responsible for eliciting humoral immune response are not important for the treatment and prevention of dental caries. Ma's data obtained from the hybrid antibodies demonstrated that for the protective effect offered by Ma's antibody, the regions responsible for eliciting humoral immune response not only can be deleted, but also can be replaced by other constant regions that do not contain a functional Fc region for eliciting humoral immune response.

The Office Action states that Ma disclosed IgG based antibodies and these IgG based antibodies, "by their very nature stimulate a humoral immune response regardless of the motivation behind its application." Applicants respectfully point out that an obviousness rejection has to rely on what is taught by the prior art, not what is inherent or allegedly inherent in the prior art.

The issue here is not whether these IgG based antibodies actually stimulated a humoral immune response or whether these IgG based antibodies can be used to stimulate a humoral immune response. What needs to be determined is whether Ma teaches or suggests the use of an antibody that functions through specific binding to the antigen and via eliciting a humoral immune response. Alternatively, the determination should be directed to whether one skilled in the art reading Ma's disclosure would have believed that in order to treat or

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[1] The Fc region includes CH2 and CH3. The constant region of IgG includes CH1, CH2, and CH3 whereas the constant region of IgA includes CH1 and CH2.

prevent dental caries, he or she should use antibodies that function via specifically binding to a cariogenic organism and via eliciting a humoral immune response.

In other words, regardless how these IgG based antibodies function "by their very nature" or what these IgG based antibodies can do "inherently", the most relevant issue to the obviousness rejection is what would have been the "take home" message to one skilled in the art based on Ma's disclosure, *e.g.*, what would have been perceived or understood by one skilled in the art reading the data and the teaching provided by Ma.

According to Ma, the protective effect of the antibody is epitope specific; whether an antibody elicits a humoral immune response is immaterial to the antibody's protective effect. Therefore, based on Ma's disclosure one skilled in the art would have used antibodies that have the same epitope specificity as Guy's 13, but would not have realized that using antibodies eliciting a humoral immune response to a cariogenic antigen could also provide protective effect for the treatment or prevention of dental caries.

Ma repeatedly teaches that "Fc-mediated functions of the mAb were not essential", "F(ab')2 portion was as protective as the intact IgG", and "functional Ig regions that are involved in complement binding and opsonization through cellular interactions are not essential." Such teaching would have directed one skilled in the art to believe that eliciting a humoral immune response was not associated with the protective effect of the antibody, thus not the functional mechanism of the antibody taught or suggested by Ma. Based on Ma's disclosure, one skilled in the art would not have been motivated to use an antibody's Fc-mediated functions in eliciting a humoral immune response through complement binding or cellular interaction for the treatment and prevention of dental caries. Therefore, the present invention is not obvious over Ma's disclosure.

Even if one skilled in the art might possibly have speculated functional mechanisms not taught or suggested by Ma, it is not likely that he or she would have speculated the humoral immune response mechanism for the antibody's protective effect. The Office Action seems to suggest that since the antibodies disclosed by Ma are IgG based, thus one skilled in the art might have thought that these antibodies could function through humoral immune response. Applicants respectfully point out that in order for an IgG antibody to trigger a humoral immune response, it has to be associated with the appropriate immune system. For example, a murine IgG antibody will not be able to work with the human

immune system to elicit a human humoral immune response. Particularly in the present case, the Fc region of murine IgG1 Guy's 13 antibody used in humans would have little or none interaction with the complement or cellular pathways of the human immune system to trigger a human humoral immune response specific to the antibody's cariogenic antigen. Therefore, one skilled in the art would have very little basis to think that humoral immune response could be the functional mechanism for the antibody's protective effect disclosed in Ma.

Furthermore, even if one skilled in the art allegedly might still have speculated that the antibodies could function possibly via eliciting a humoral immune response, he or she would not have had any reasonable expectation of success by relying on the humoral immune response mechanism in light of Ma's teaching. Ma clearly does not suggest such functional mechanism and has concluded that Ig regions involved in humoral immune response are not essential and deletion of these regions responsible for the functions has no impact on the protective effect of the antibody. (See page 131, last paragraph and page 136, last paragraph.) Ma's disclosure strongly suggests that humoral immune response is not the functional mechanism for the antibodies disclosed and effectively teaches away from using antibodies with this functional mechanism for the treatment and prevention of dental caries. Therefore, the present invention is not obvious over Ma's disclosure.

In summary, Ma does not teach or suggest using the antibody to elicit a humoral immune response for the treatment or prevention of dental caries. Ma concludes that the Ig regions responsible for eliciting a humoral immune response are dispensable since deletion of these regions made no impact on the protective effect of the antibody. Therefore, Ma does not teach or suggest the methods provided by the present invention and in effect teaches away from the mechanism required by the present invention.

Adair is cited as a secondary reference. Adair discloses the making of a humanized antibody against carcinoembryonic antigen. Adair does not cure the deficiency of Ma because it too fails to teach or suggest using chimeric antibodies to treat dental caries, especially by eliciting a humoral immune response.

In conclusion, the present invention is not obvious over Ma in view of Adair. Withdrawal of the rejection of claims 1-4, 6-10, 12 and 17 under 35 U.S.C. § 103 is respectfully requested.

In view of the amendment and the above remarks, it is submitted that the claims are in condition for allowance and a notice to that effect is respectfully requested. The Examiner is invited to contact Applicants' undersigned representative if there are any questions relating to this application.

Please charge any additional fees, or make any credits, to Deposit Account No. 07-1895.

Respectfully submitted,

Date: 9/24/02

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Enclosures: Exhibit A

EXHIBIT A

CLAIMS UPON ENTRY OF THE AMENDMENT

1. A method for the treatment and prevention of dental caries in a mammal comprising oral administration of a chimeric monoclonal antibody that specifically binds to a cariogenic organism and elicits a humoral immune response to an antigen displayed by the cariogenic organism from the mammal, wherein the portion of the monoclonal antibody that binds to the cariogenic organism is derived from a species other than that of the mammal to be treated.

2. The method for treatment and prevention of dental caries of claim 1 wherein the chimeric monoclonal antibody is produced by the steps of:

a) inoculating a mammalian host with the cariogenic organism;

b) identifying a hybridoma from the mammalian host that secrete a monoclonal antibody specific to the antigen displayed by the cariogenic organism; and

c) preparing the chimeric monoclonal antibody comprising a complementarity-determining region from the monoclonal antibody of step b) above and a constant domain from the mammal to be treated.

3. (Amended) The method for treatment and prevention of dental caries of claim 2 wherein step c) further comprises synthesis of a nucleic acid construct comprising:

a) a nucleic acid sequence that codes on expression for the complementarity determining region of the monoclonal antibody; and

b) a nucleic acid sequence that codes on expression for the constant domain of an antibody selected from the group

consisting of class IgG and class IgM of the mammal to be treated.

4. The method for treatment and prevention of dental caries of claim 3 wherein the chimeric monoclonal antibody is expressed by a eukaryotic host that has been transformed with the nucleic acid construct of claim 3 above.

5. (Cancelled) The method for treatment and prevention of dental caries in a mammal of claim 4, wherein the monoclonal antibody is administered by oral ingestion of tissue from a eukaryotic host transformed with the nucleic acid construct of claim 4 above.

6. The method for treatment and prevention of dental caries of claim 1 wherein the mammal to be treated is human, and the other species is mouse.

7. A method for treatment and prevention of dental caries in a mammal comprising administration to a subject in need of such treatment a chimeric monoclonal antibody that specifically binds to a cariogenic organism and elicits a humoral immune response to an antigen displayed by the cariogenic organism from the mammal, wherein the portion of the monoclonal antibody that binds to the cariogenic organism is derived from a species other than that of the mammal to be treated.

8. The method for treatment and prevention of dental caries of claim 7 wherein the monoclonal antibody is produced by the steps of:

a) inoculating a mammalian host with the cariogenic organism;

b) identifying a hybridoma from the mammalian host that secrete a monoclonal antibody specific to the antigen displayed by the cariogenic organism; and

c) preparing a chimeric monoclonal antibody comprising a complementarity-determining region from the monoclonal

antibody of step b) above and a constant domain from the mammal to be treated.

9. (Amended) The method for treatment and prevention of dental caries of claim 8 wherein the step c) further comprises preparation of a nucleic acid construct that includes:

a) a nucleic acid sequence that codes on expression for the complementarity determining region of the monoclonal antibody; and

b) a nucleic acid sequence that codes on expression for the constant domain of an antibody selected from the group consisting of class IgG and class IgM of the mammal to be treated.

10. The method for treatment and prevention of dental caries of claim 9 wherein the chimeric monoclonal antibody is expressed by a eukaryotic host that has been transformed with the nucleic acid construct of claim 9 above.

11. (Cancelled) The method for treatment and prevention of dental caries in a mammal of claim 9, wherein the monoclonal antibody is administered by oral ingestion of tissue from a eukaryotic host that has been transformed with the nucleic acid construct of claim 9 above.

12. The method for treatment and prevention of dental caries of claim 8, wherein the mammalian host is a mouse, and the mammal to be treated is a human.

13. (Cancelled) The method for treatment and prevention of dental caries of claim 5 wherein the eukaryote is a plant.

14. (Cancelled) The method for treatment and prevention of dental caries of claim 5 wherein the eukaryote is a plant of the species *Brassica*.

15. (Cancelled) The method for treatment and prevention of dental caries of claim 11 wherein the eukaryote is a plant.

16. (Cancelled) The method for treatment and prevention of dental caries of 5 claim 11 where the eukaryote is a plant of the species *Brassica*.

17. The method for treatment and prevention of dental caries of claim 8, wherein the mammal to be treated is a dog or a cat.